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Early Post-Transplant Serum Ferritin Levels as Predictive Biomarkers for Severe Acute Graft-Versus-Host Disease in Pediatric Umbilical Cord Blood Transplantation for Acute Leukemia

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) using umbilical cord blood is a valuable therapy option for patients with acute leukemia (AL). Acute graft-versus-host disease (aGVHD) remains the most frequently encountered complication. This study investigated risk factors for aGVHD and assessed whether post-transplant serum ferritin (SF) within 2 weeks is a potential biomarker for aGVHD in pediatric patients with AL undergoing umbilical cord blood transplantation (UCBT).

Material/Methods: We conducted a retrospective cohort study of 71 patients with AL who underwent UCBT at the Children's Hospital of Soochow University between 2017 and 2022. We evaluated several factors related to aGVHD. Univariate and multivariate analyses were performed using the proportional subdistribution hazard regression model of Fine and Gray. Analyses of overall survival (OS) were performed using the Kaplan-Meier method, and differences were compared using log-rank tests.

Results: Of the 71 patients, 23 (32.4%) experienced grade II-IV aGVHD, of whom 18 (25.4%) developed grade III-IV aGVHD. Patients with grade II-IV and III-IV aGVHD had worse 5-year OS (69.4±10%, p=0.01; and 60.6±11.6, *P*=0.007, respectively). Conditioning intensity was a risk factor for grade III-IV aGVHD (HR: 0.34, 95% CI: 0.13-0.89, *P*=0.027). An SF level >1650 ng/mL within 2 weeks post-transplant was associated with an increased risk of severe aGVHD (HR: 3.61, 95% CI: 1.09-11.97, *P*=0.036).

Conclusions: Post-transplant SF within 2 weeks was a potential biomarker for developing severe aGVHD. Higher levels of post-transplant SF are associated with a higher incidence of grade II-IV aGVHD and grade III-IV aGVHD.

Keywords: Hospitals, Pediatric • Cord Blood Stem Cell Transplantation • Graft vs Host Disease • Ferritins

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a valuable therapy option for patients with acute leukemia (AL). Umbilical cord blood, as a conveniently available donor source with low immunogenicity and less stringent human leukocyte antigen (HLA)-matching requirements, has emerged as an alternative donor source because of the scarcity of HLA-matched related donors [1,2]. Although the outcomes of umbilical cord blood transplantation (UCBT) have considerably improved, acute graft-versus-host disease (aGVHD) remains the most common and potentially life-threatening complication [3,4]. The risk factors for aGVHD and outcomes of aGVHD in adults using conventional donor sources are well documented. HLA matching, sex disparity between the donor and recipient, conditioning intensity, increased age, multiparous female donors, ineffective aGVHD prophylaxis, graft source, gut bacterial diversity, and total body irradiation have been implicated as risk factors for the onset of aGVHD [5-10]. However, little is known about risk factors for aGVHD after UCBT in children, and it is unclear whether the risk factors and outcomes are similar to those of conventional donor sources in adults.

Patients undergoing allo-HSCT are often transfused with multiple units of blood products, which can result in iron overload. Serum ferritin (SF) is an acute-phase reactant protein which can become elevated in response to iron overload. SF levels have been shown to correlate with long-term outcomes. According to a meta-analysis of 25 trials involving 4545 patients, a high pretransplant SF level was associated with worse overall survival (OS) [11]. Elevated post-transplant SF levels have also been linked to increased non-relapse mortality and lower OS [12-14]. Furthermore, Lin et al [15] demonstrated that increased pretransplant SF levels are linked to a higher incidence of grade II-IV aGVHD and grade III-IV aGVHD in patients with severe aplastic anemia (SAA). However, the relationship between post-transplant SF and aGVHD in children with AL after UCBT is yet to be clarified.

Therefore, we performed a retrospective study at our center to analyze the outcomes of aGVHD and possible risk factors in pediatric patients with AL after UCBT. The purpose was to identify risk factors for aGVHD to improve the quality of life after UCBT in children with AL.

Material and Methods

Patients

This study included children aged 1-18 years diagnosed with AL who underwent UCBT at Children's Hospital of Soochow University, Suzhou, China, from 2017 to 2022. The patients' parents and stem cell donors provided written informed consent before beginning the transplantation process. The patient selection criteria were as follows: (i) diagnosis of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or mixed phenotype acute leukemia (MAL); (ii) aged 0-18 years at the time of transplantation; (iii) received a single-unit of cord blood; (iv) no prior allo-HSCT; and (v) neutrophils were successfully engrafted.

Supportive Care

Calcineurin inhibitors (cyclosporine or tacrolimus) were used in combination with methotrexate or mycophenolate mofetil for GVHD prophylaxis. All patients were given routine supportive treatment, including antiviral (acyclovir) prophylaxis for herpes simplex virus-positive recipients, preemptive cytomegalovirus prophylaxis, and antifungal prophylaxis.

Definitions

AGVHD was diagnosed and graded according to previously published consensus guidelines [16]. OS considered death from any cause as the event, and surviving patients were censored at the date of last contact. Neutrophil engraftment was defined as an absolute neutrophil count $\geq 0.5\times10^9$/L for ≥3 days. Platelet engraftment was defined as platelet count $\geq 20\times10^9$/L without transfusion support for ≥7 days.

Statistical Analysis

To compare differences between groups, the chi-square test and Mann–Whitney U test were used to assess the statistical significance of differences in categorical and continuous variables, respectively, between groups. Univariate and multivariable analyses were performed using Gray's test and the Fine and Gray proportional subdistribution hazards regression model. Death before day 180 without severe aGVHD was considered a competing event. Variables with $P<0.10$ were included in the multivariable model. OS was estimated using the Kaplan-Meier method, and differences were compared using log-rank tests. The statistical analyses were performed using RStudio software (version 4.3.1; RStudio Team, Boston, MA, USA; URL: http://www.rstudio.com/).

Results

Outcomes of Acute Graft-Versus-Host Disease

We compared the OS and relapse-free survival (RFS) of the patients between groups of different grades of aGVHD. This study did not find a statistically significant difference in the OS and RFS of patients with grade I-IV aGVHD (**Figure 1**). However, patients with grade II-IV or grade III-IV aGVHD had worse OS (**Figures 2 and 3**, 69.4±10%, $P=0.01$ and 60.6± 11.6%, $P=0.007$, respectively).

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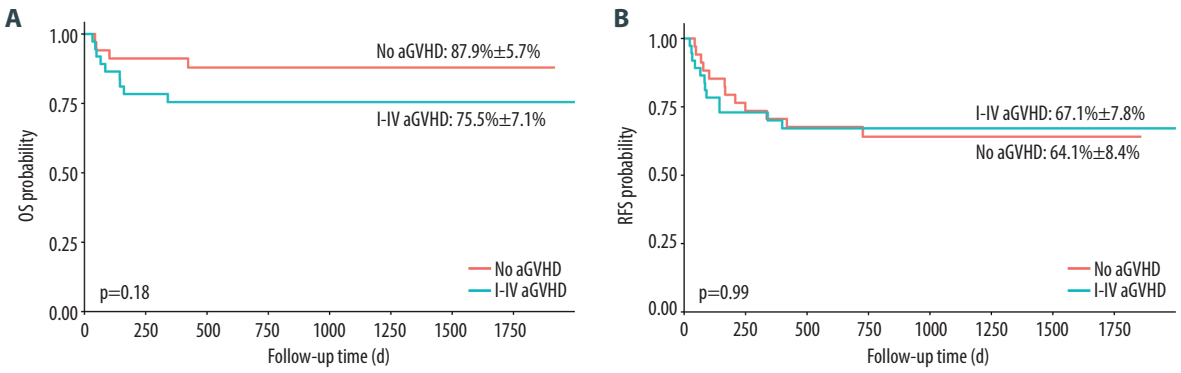

Figure 1. Overall survival (OS) and relapse-free survival (RFS) in patients with and without acute graft-versus-host disease (aGVHD). (**A**) OS in patients with grade I-IV aGVHD vs no (grade 0) aGVHD; (**B**) RFS in patients with grade I-IV aGVHD vs no (grade 0) aGVHD. aGHVD – acute graft-versus-host disease; OS – overall survival; RFS – relapse-free survival. *Software used for the creation of the figure: RStudio (version 4.3.1, Microsoft).*

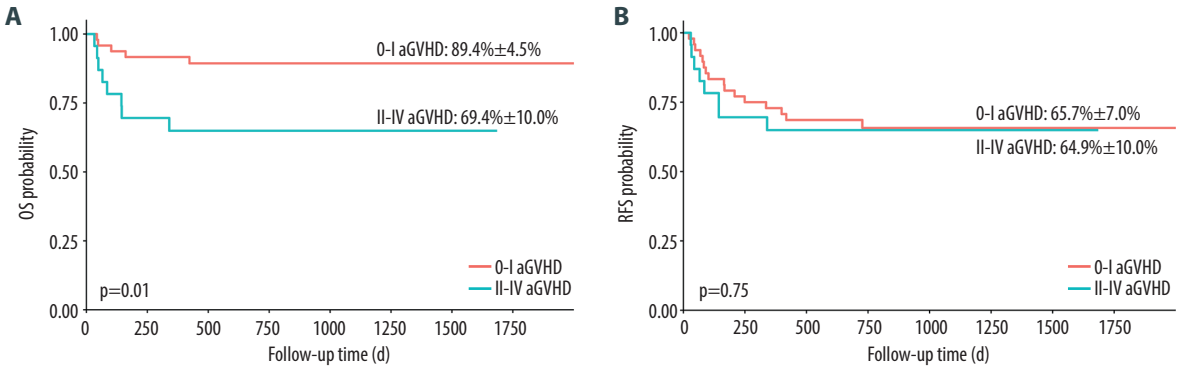

Figure 2. Overall survival (OS) and relapse-free survival (RFS) in patients with and without acute graft-versus-host disease (aGVHD). (**A**) OS in patients with grade II-IV aGVHD vs grade 0-I aGVHD; (**B**) RFS in patients with grade II-IV aGVHD vs grade 0-I aGVHD. aGHVD – acute graft-versus-host disease; OS – overall survival; RFS – relapse-free survival. *Software used for the creation of the figure: RStudio (version 4.3.1, Microsoft).*

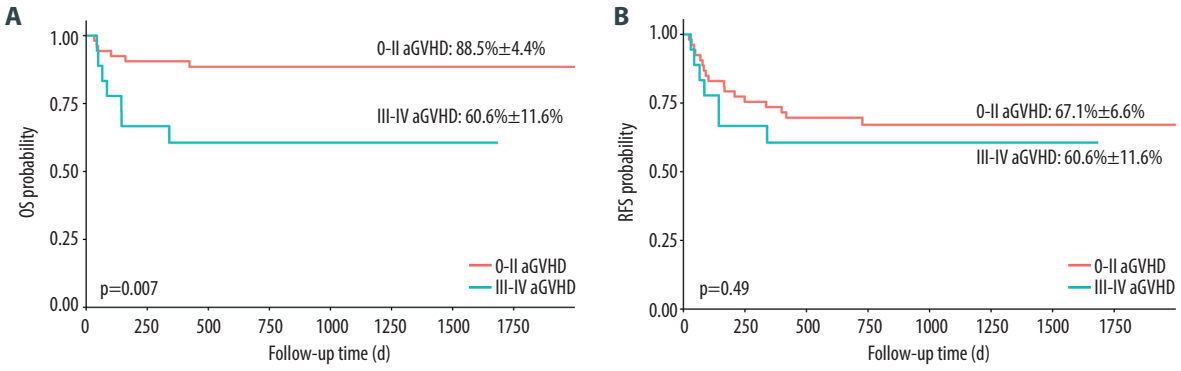

Figure 3. Overall survival (OS) and relapse-free survival (RFS) in patients with and without acute graft-versus-host disease (aGVHD). (**A**) OS in patients with grade III-IV aGVHD vs grade 0-II aGVHD; (**B**) RFS in patients with grade III-IV aGVHD vs grade 0-II aGVHD. aGHVD – acute graft-versus-host disease; OS – overall survival; RFS – relapse-free survival. *Software used for the creation of the figure: RStudio (version 4.3.1, Microsoft).*

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Characteristics of Patients with Grade 0-II and III-IV Acute Graft-Versus-Host Disease

The patients were divided into 2 groups: grade 0-II and grade III-IV aGVHD. The characteristics of patients in each group are shown in **Table 1**. The grade 0-II aGVHD group included 53 patients (27 boys and 26 girls) with a median age of 3.58 years (range: 0.67-12.57 years). There were 30 patients with AML and 23 patients with ALL. The median doses of mononuclear cells (MNC) and $CD34^+$ cells were 6.20×10^7/kg (range: $1.30\text{-}11.33\times10^7$/kg) and 2.73×10^5/kg (range: $1.70\text{-}6.41\times10^5$/kg), respectively. The grade II-IV aGVHD group included 18 patients (8 boys and 10 girls) with a median age of 3.98 years (range: 1.42-8.83 years), 8 with AML, 8 with ALL, and 2 with MAL. The median doses of MNC and $CD34^+$ cells were 5.90×10^7/kg (range: $1.37\text{-}11.79\times10^7$/kg) and 2.78×10^5/kg (range: $0.83\text{-}9.20\times10^5$/kg), respectively.

Risk Factors for Grade III-IV Acute Graft-Versus-Host Disease

We assessed several other variables for a potential association with an increased risk of III-IV aGVHD using univariate analysis, including age, sex, disease, HLA matching, ABO matching, disease status at transplant, conditioning intensity, anti-thymocyte globulin (ATG), conditioning drug dose, neutrophil engraftment time, platelet engraftment time, MNC, $CD34^+$, post-transplant SF within 2 weeks (all before aGVHD occurred), and pretransplant SF (**Table 2**). HLA matching (hazard ratio [HR]: 0.46, 95% CI: 0.18-1.14, *P*=0.093), conditioning intensity (HR: 0.32, 95% CI: 0.13-0.81, *P*=0.017), and SF level within 2 weeks post-transplant (HR: 3.98, 95% CI: 1.16-13.60, *P*=0.028) were associated with an elevated risk of developing III-IV aGVHD. Furthermore, conditioning intensity (HR: 0.34, 95% CI: 0.13-0.89, *P*=0.027) and SF level within 2 weeks post-transplant (HR: 3.61, 95% CI: 1.09-11.97, *P*=0.036) were independent risk factors for severe aGVHD in the multivariable analysis.

Acute Graft-Versus-Host Disease After Umbilical Cord Blood Transplantation

Seventy-one patients were included in the analysis, of whom 37 were in the aGVHD group (14 with grade I aGVHD, 5 with grade II aGVHD, 3 with grade III aGVHD, and 15 with grade IV aGVHD). The sites involved included the skin (31 patients), intestines (22 patients), and liver (10 patients). The patients were divided into 2 groups according to their SF level (**Table 3**).

Incidence of Acute Graft-Versus-Host Disease

The incidence of grade II-IV was 44.4% in patients with an SF level >1650 ng/mL, as opposed to 14.3% in patients with an SF level <1650 ng/mL, representing a statistically significant difference (*P*=0.011). Similarly, for grade III-IV aGVHD, the incidence was 35.4% in patients with an SF level >1650 ng/mL and 10.7% in patients with an SF level <1650 ng/mL (*P*=0.024) (**Figure 4**).

Outcomes According to Serum Ferritin Levels

Finally, we compared the OS and RFS of patients in the SF level <1650 ng/mL and >1650 ng/mL groups. OS and RFS were not associated with the SF level (**Figure 5**, *P*=0.15 and *P*=0.058, respectively).

Discussion

This study assessed the prognosis of children with aGVHD after UCBT and identified risk factors for the development of grades III-IV aGVHD. In recent years, an increasing number of children with AL have undergone UCBT. Despite significant developments in UCBT, aGVDH remains a crucial factor restricting quality of life, especially in patients with severe aGVHD. Patients with grade II-IV and III-IV aGVHD had worse 5-year OS. Infection is the cause of death in most patients with aGVHD, which may have been exacerbated by more aggressive immunosuppressive strategies. Consequently, it is critical to understand the risk factors for aGVHD.

Several risk factors for aGVHD in patients undergoing UCBT, such as myeloablative conditioning, omission of ATG, and double umbilical cord blood, have been described previously [10,17-19]. In this study, we similarly found that conditioning intensity was an independent risk factor for III-IV aGVHD. We also identified the post-transplant SF level as a risk factor for severe aGVDH in the univariate and multivariable analysis.

Previous studies have found that the maximum post-transplant SF levels were significantly higher in patients during aGVHD after allo-HSCT [20]. However, it remains unclear whether post-transplant SF is associated with the occurrence of aGVHD after UCBT in children with AL. We found the post-transplant SF level within 2 weeks was a potential biomarker for predicting development of severe aGVHD. The SF level was also associated with the incidence of II-IV and III-IV aGVHD.

There are multiple potential causes of hyperferritinemia in patients undergoing UCBT. Brissot et al [21] reported that hyperferritinemia can be caused by inflammation, metabolic syndrome, hepatitis, and alcoholism. Iron overload can also induce hyperferritinemia after allo-HSCT, which may be related to transfusions, dyserythropoiesis, or associated genetic factors, and has been reported as a risk factor for aGVHD [22].

Ferritin can have an impact on effects of antigen presenting cells [23]. The activation of antigen-presenting cells is the main

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Table 1. Baseline characteristics of patients with grade 0-II and grade III-IV acute graft-versus-host disease.

Variable	Grade 0-II aGVHD (n=53)	Grade III-IV aGVHD (n=18)	P value
Recipient age in years, median (range)	3.58 (0.67-12.57)	3.98 (1.42-8.83)	0.463
Sex			0.634
Male, n (%)	27 (51%)	8 (44%)	
Female, n (%)	26 (49%)	10 (56%)	
Disease			0.053
AML, n (%)	30 (57%)	8 (44%)	
ALL, n (%)	23 (43%)	8 (44%)	
MAL, n (%)	0 (0%)	2 (12%)	
HLA matching			0.076
≥9/10, n (%)	36 (68%)	8 (44%)	
<9/10, n (%)	17 (32%)	10 (56%)	
ABO matching			0.663
Matched, n (%)	12 (23%)	5 (28%)	
Mismatched, n (%)	41 (77%)	13 (72%)	
Disease status at transplant			0.405
CR1, n (%)	32 (60%)	13 (72%)	
CR2, n (%)	11 (21%)	2 (11%)	
PR, n (%)	7 (13%)	3 (17%)	
NR, n (%)	3 (6%)	0 (0%)	
Conditioning intensity			0.037
MAC, n (%)	43 (81%)	10 (56%)	
RIC, n (%)	10 (19%)	8 (44%)	
ATG			0.340
Yes, n (%)	11 (21%)	2 (11%)	
No, n (%)	42 (79%)	16 (89%)	
Conditioning drug dose median (range)			
Bu, mg/kg	12.31 (8.64-14.20)	12.80 (8.40-14.10)	0.450
CTX, mg/kg	120.00 (75.79-141.00)	120.00 (72.00-141.18)	0.317
Neutrophil engraftment time, median (range), days	15.00 (10.00-29.00)	15.00 (12.00-23.00)	0.680
Platelet engraftment time, median (range), days	31.00 (13.00-43.00)	27.50 (11.00-56.00)	0.277
Total infused cell count, median (range)			
MNC, $\times 10^7$/kg	6.20 (1.30-11.33)	5.90 (1.37-11.79)	0.895
CD34+, $\times 10^5$/kg	2.73 (1.70-6.41)	2.78 (0.83-9.20)	0.648

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Table 1 continued. Baseline characteristics of patients with grade 0-II and grade III-IV acute graft-versus-host disease.

Variable	Grade 0-II aGVHD (n=53)	Grade III-IV aGVHD (n=18)	P value
SF level within 2 weeks post-transplant			0.022
>1650 ng/mL, n (%)	28 (53%)	15 (83%)	
<1650 ng/mL, n (%)	25 (47%)	3 (17%)	
SF level within 2 weeks pretransplant			0.251
>1650 ng/mL, n (%)	6 (11%)	4 (22%)	
<1650 ng/mL, n (%)	47 (89%)	14 (78%)	

aGVHD – acute graft-versus-host disease; ALL – acute lymphocytic leukemia; AML – acute myeloid leukemia; ATG – anti-thymocyte globulin; Bu – busulfan; CI – confidence interval; CR – complete response; CTX – cyclophosphamide; HR – hazard ratio; MAL – mixed phenotype acute leukemia; MNC – mononuclear cells; NR – no response; PR – partial response; SF – serum ferritin.

Table 2. Risk factors for the occurrence of III-IV acute graft-versus-host disease in pediatric patients undergoing allogeneic hematopoietic stem-cell transplantation.

Risk factors	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.99	0.89-1.12	0.920			
Sex female vs male	1.27	0.51-3.17	0.600			
Disease (AL type)	1.94	0.80-4.73	0.140			
HLA matching	0.46	0.18-1.14	0.093*	0.45	0.18-1.17	0.100
ABO matching	1.27	0.46-3.51	0.640			
Disease status at transplant						
CR1	1.65	0.61-4.48	0.330			
CR2	0.51	0.12-2.17	0.360			
PR	1.19	0.37-3.84	0.770			
NR	Reference					
Conditioning intensity	0.32	0.13-0.81	0.017*	0.34	0.13-0.89	0.027
ATG	0.50	0.12-2.04	0.330			
Conditioning drug dose						
Bu	0.92	0.69-1.23	0.560			
CTX	0.98	0.95-1.02	0.340			
Neutrophil engraftment time	1.00	0.90-1.12	0.950			
Platelet engraftment time	1.01	0.97-1.05	0.610			
Total infused cell count						
MNC	1.03	0.85-1.24	0.800			
CD34+	1.01	0.81-1.27	0.900			
SF level within 2 weeks post-transplant	3.98	1.16-13.60	0.028*	3.61	1.09-11.97	0.036
SF level within 2 weeks pretransplant	1.97	0.66-5.89	0.220			

AL – acute leukemia; ATG – anti-thymocyte globulin; Bu – busulfan; CI – confidence interval; CR – complete response; CTX – cyclophosphamide; HR – hazard ratio; MNC – mononuclear cells; NR – no response; PR – partial response; SF – serum ferritin.

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Table 3. Characteristics of pediatric patients with acute graft-versus-host disease according to their serum ferritin level.

		Serum ferritin level	
	Total	>1650 ng/mL	<1650 ng/mL
aGVHD classification			
Grade I, n	14	8	6
Grade II, n	5	4	1
Grade III, n	3	2	1
Grade IV, n	15	13	2
aGVHD target organ			
Skin aGVHD, n	31	22	9
Intestinal aGVHD, n	22	19	3
Hepatic aGVHD, n	10	9	1

aGVHD – acute graft-versus-host disease.

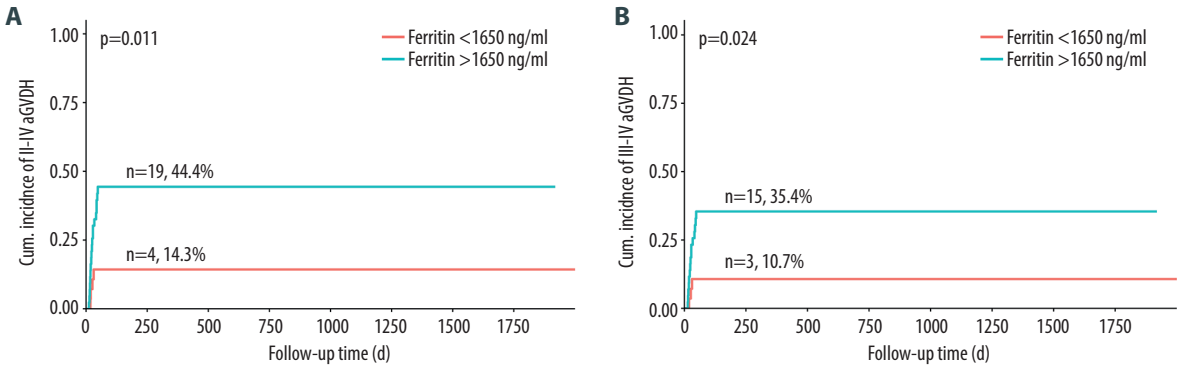

Figure 4. (**A, B**) Cumulative incidence of grades II-IV and III-IV aGVHD in patients with a serum ferritin level >1650 ng/mL and <1650 ng/mL. *Software used for the creation of the figure: RStudio (version 4.3.1, Microsoft).*

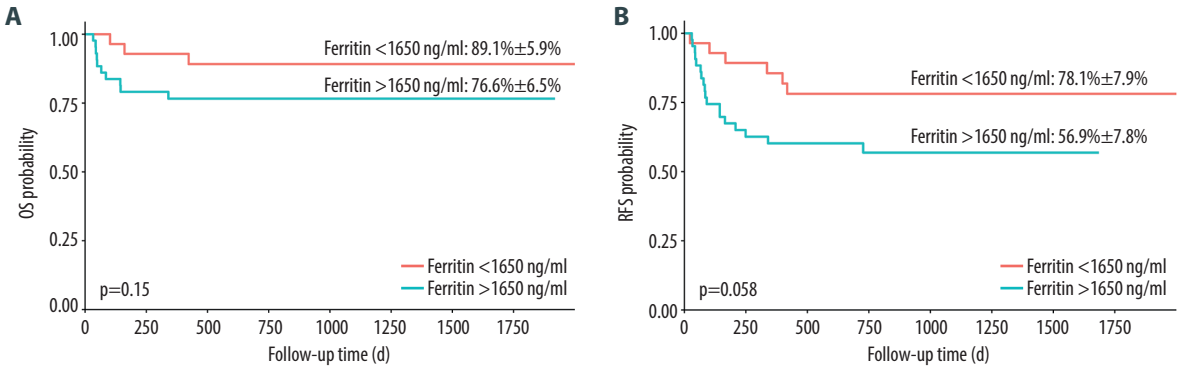

Figure 5. (**A, B**) Overall survival and relapse-free survival of patients with serum ferritin levels <1650 ng/mL and >1650 ng/mL. OS – overall survival; RFS – relapse-free survival. *Software used for the creation of the figure: RStudio (version 4.3.1, Microsoft).*

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mechanism of aGVDH pathogenesis. Furthermore, ferritin enhances the susceptibility to aGVHD by organ toxicity due to reactive oxygen species [24]. Several in vivo studies have demonstrated that mitigating iron overload could potentially reduce the incidence of aGVHD [25,26].

In a retrospective analysis, Lin et al [15] found that pretransplant SF levels were a risk factor for aGVHD in patients with SAA after allo-HSCT. However, we found that the pretransplant SF level was not an independent predictor of aGVHD after UCBT in children with AL. This may be due to the absence of the need for repeated transfusions in patients with AL compared with patients with SAA before UCBT, which may result in no obvious elevation of pretransplant SF. Several studies have shown that post-transplant SF can be used to predict survival outcomes [12-14,27]. Nevertheless, the 5-year OS and RFS did not differ significantly according to the SF level in our analysis. This may be attributable to the limited sample size.

This study has some limitations, including the retrospective design and limited number of patients included in the analysis. Prospective multicenter trials are needed to confirm the risk factors for aGVHD after UCBT in children with AL.

Conclusions

In conclusion, the post-transplant SF level within 2 weeks was a potential biomarker for developing severe aGVHD. Higher levels of post-transplant SF are associated with a higher incidence of grade II-IV aGVHD and grade III-IV aGVHD. However, these results need to be confirmed in prospective studies.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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